AD_____

GRANT NO. DAMD17-94-J-4261

TITLE: Effect of a Stress Reduction Intervention on Psycho-Immuno-Endocrine Parameters in Early Stage Breast Cancer

PRINCIPAL INVESTIGATOR(S): Ann O. Massion, M.D.

CONTRACTING ORGANIZATION: University of Massachusetts Medical Center
Worcester, Massachusetts 01655

REPORT DATE: December 28, 1995

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick,. Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	December 28, 1995	Annual (30 Sep 94 - 29 Sep 95)

4. TITLE AND SUBTITLE
Effect of a Stress Reduction Intervention on Psycho-Immuno-Endocrine Parameters in Early Stage Breast Cancer

5. FUNDING NUMBERS
DAMD17-94-J-4261

6. AUTHOR(S)
Ann O. Massion, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Massachusetts Medical Center
Worcester, MA 01655

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

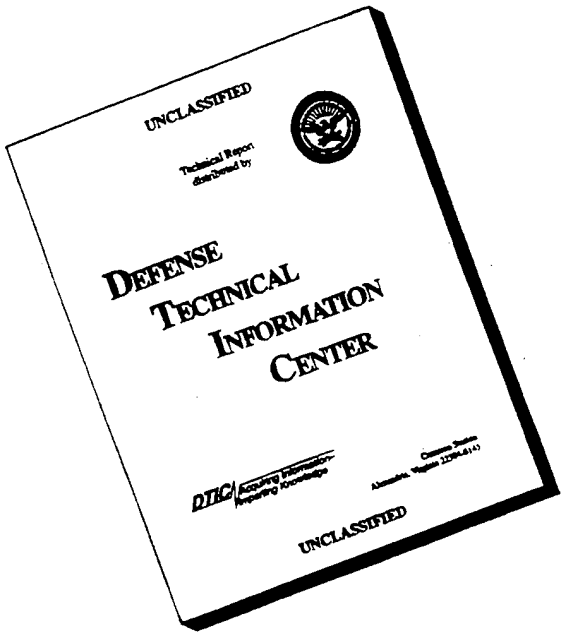
12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200* The Breast Research Initiative for Determining Effective Skills for coping with cancer (BRIDGES) consists of a prospective, randomized intervention trial with 60 women in each of three arms 1) the UMass mindfulness mediation-based Stress Reduction and Relaxation Program (SR&RP); 2) a nutrition education program (NEP) developed specifically for BRIDGES; and 3) a usual care control group. The 180 women under age 65 with Stage I or Stage II breast cancer enrolling into this randomized trial are being evaluated for: 1) psychological and behavioral indices of function and coping 2) Quality of Life (QOL) measures, 3) compliance with the interventions and with medical treatment regimes, and 4) biochemical/immunological measures consisting of cytokines and melatonin. Analyses will be conducted to test hypotheses related to the three specific aims of the study. SR&RP effect on QOL; SR&RP & NEP effects on immune parameters, and durability/decay of intervention-related effects. As of 30 Sep 19, the study had closely adhered to the SOW agreed upon at the time the grant was awarded. Recruitment has achieved and is maintaining targeted levels. All subjects who have begun the study have been retained. All data has been collected.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer, Psychosocial Intervention, Meditation, Relaxation Technique, Quality of Life, Melatonin, Nutrition	9
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

DISCLAIMER NOTICE



THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

( ) Where copyrighted material is quoted, permission has been obtained to use such material.

( ) Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

( ) Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

( ) In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

( ) For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 32 CFR 219 and 45 CFR 46.

( ) In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

M.D.
Principal Investigator's Signature

ANN O. MASSION, M.D.

12-28-95
Date

TABLE OF CONTENTS

INTRODUCTION

An increasing body of research literature has shown that psychological states have clear impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping styles, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. There also is a small body of evidence indicating that women with breast cancer receiving psychosocial interventions may derive a beneficial effect in respect to improved response and disease-free survival. Psychological distress seems to be particularly acute in younger women with breast cancer, a population that seems particularly amenable to psychosocial interventions. This is due, in part, to the fact that breast cancer tends to be a more aggressive disease of young ages and younger women have more concern with issues related to body image and major disruptions to typically very busy lives.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. A successful intervention will be one that can reduce emotional distress, promote effective coping with diagnosis and treatment for breast cancer, and be useful and adaptable to the diverse population of younger women with breast cancer. The current study seeks to adapt the University of Massachusetts Medical Center's Stress Reduction and Relaxation Program (SR&RP) for younger women with breast cancer. The SR&RP is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educationally based. Currently, it functions in inner city health clinics with diverse populations.

Our research addresses aspects of two of the fundamental research issues in psychosocial effects of breast cancer and the role of our well-recognized (but hitherto untested in this population of patients) SR&RP intervention in quality of life and status of immune parameters that may themselves be important in determining disease prognosis. Specifically, this research is designed to: 1) examine the psychosocial impact of breast cancer; and 2) identify techniques for delivering cost-effective care to facilitate recovery, improve immunological response, and improve quality of life after treatment for breast cancer.

Overall Goal

The primary goal of this proposal is to test the efficacy of the well-established, short-duration mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP) in women under 65 years old with newly diagnosed Stage I and Stage II breast cancer. The SR&RP intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for: adjustment to a potentially life-threatening diagnosis; enhancement of quality of life; and potentially, for enhancement of resistance to disease progression and survival in women with breast cancer. The study will consist of a prospective randomized three-arm design with 60 women enrolled into each arm: 1)

the SR&RP intervention, tailored to focus on issues specific to this population; 2) a nutrition education program (NEP) which will serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on immune parameters (see Specific Aim 2); and 3) a usual care control group.

Specific Aim 1: To test the effect of SR&RP on Quality of Life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and with medical recommendations in women (under 65 years old) with newly diagnosed Stage I and II breast cancer. Because the SR&RP and NEP groups will have an equally intense group session component and the NEP group will receive none of the essential components of the SR&RP, the test between the two groups, SR&RP and NEP, will distinguish between the effect of the SR&RP intervention and non-specific group/therapist factors.

Primary Hypothesis: The SR&RP intervention will result in improved QOL and ability to cope, compared either to the NEP or to usual care alone.

Secondary Hypothesis: The SR&RP intervention will result in: a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Specific Aim 2: To test the relative effect of the SR&RP versus NEP and usual care on immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels that may in turn affect response to breast cancer (1). Because NK activity may be related to recurrence (2) we have previously shown that low-fat diets enhance NK activity (3) and we have preliminary data that meditation may affect melatonin levels in women, we are particularly interested in relative differences between the two test groups, SR&RP and NEP, compared to usual care alone.

Specific Hypothesis: Relative to usual care, the SR&RP intervention will increase the immune responsiveness of Stage I and II breast cancer patients. This will result in an increase in the production of cytokines, e.g., Interlenkins 2 and 4 (IL-2,4), which activate NK cells, and interferon (IFN) γ, which activates macrophages.

Specific Aim 3: To determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

Specific Hypothesis: Psychosocial and immunological changes will be maintained over time and related to on-going practice of the SR&RP and NEP dietary practices, self-regulatory strategies and behaviors.

WORK ACCOMPLISHED

A statement of the work accomplished for the overall project was provided as part of Dr. Hebert's report. Therefore I will focus this section on my particular role and tasks as part of the project.

Task One: Run-in phase, Months 1-3

a. I attended weekly meetings during the first approximately 6 months of the study. The meetings were attended at various times by site coordinators from the four participating sites, the Principal Investigator, Project Coordinator, and other investigators. I also chaired or participated in sub-committees involved in: 1) developing screening questions and baseline questionnaires to be used in recruiting and at the baseline assessment; 2) writing the script for the recruiting videotape and being involved in producing the videotape which was then used at the participating sites; 3) writing and producing other recruitment materials such as the brochure and descriptions of the individual interventions themselves; 4) developing the intervention protocol for the stress reduction intervention; 4) developing the actual recruitment procedure with specific modifications for each site.

b. With regard to development of the stress reduction intervention protocol: decisions were made about integrating separate sessions composed only of women in the study with the larger sessions provided as part of the standard stress reduction program already offered at the University of Massachusetts Medical Center. The larger sessions are composed of 30-40 people with a wide variety of medical or psychiatric problems, not just breast cancer. The smaller sessions are composed of 6-12 women, all of whom are in the study. The decision was made to have the smaller groups specific for women in the study occur with two sessions before the standard stress reduction series and 4 sessions after the completion of the series. The purpose of these sessions, which were "wrapped around" the standard stress reduction program, is to reinforce the practices taught in the program and give the women a chance to talk about issues specific to breast cancer.

c. With regard to the recruitment and intervention protocols: development of the protocol also included researching the effectiveness of recruitment methods used in other studies similar to ours and contacting an investigator from a major study who was able to provide valuable information. Also, we conducted our own preliminary focus group with a community-based breast cancer support group in order to gather data that would inform certain decisions such as timing of recruitment, and timing and length of the intervention itself. I conducted the focus group with another investigator. This data was then used in developing the recruitment protocol as well as the intervention protocol.

d. I researched and developed the procedure for collection of 24 hour urine specimens and delivery of the specimens to the laboratory which is conducting the melatonin assays for the study. Also, I oversaw a trial run of assays which was conducted by the laboratory using samples from a preliminary study which I conducted with another co-investigator. This included working with the laboratory technician and Project Coordinator to ensure that the

assay procedure was feasible and to resolve any potential problems with it.

Task Two: Recruitment, Months 4-21:

a. I conducted an investigation of two of the participating sites to determine the best strategy by which potential subjects could be identified for recruitment. This involved identifying all the clinics and satellite clinics at the sites where women with breast cancer were diagnosed, and the reporting systems for the diagnosis. Also, I worked with the Project Coordinator who was conducting a similar investigation at the University of Massachusetts Medical Center site. As as result of these investigations, we were able to determine how to facilitate and maximize our recruitment capability. Lastly, I was involved in meetings with the PI Dr. Hebert, the Project Coordinator, and other investigators, in which the decision was made to extend the age eligibility to age 65 or less.

Currently, I am still involved in facilitating recruitment by maintaining contact with the various sites and investigating ways to improve the recruitment protocol.

b. As of 12-19-95, 97 women have been enrolled into the study. This represents slightly more than 50% of the total recruitment.

c. I have been involved in planning and participating in quarterly Steering Committee meetings which involve the Study PI, Study Coordinator, site coordinators, and other personnel involved in the study. These meetings will be ongoing throughout the study.

Task Three: Intervention, months 6-27:

a. During the first intervention cycle, I and another co-investigator provided the 6 "wrap-around" or booster sessions for the women randomized to the stress reduction intervention arm. Beginning with the second intervention cycle, I began providing the 6 sessions alone and will continue to do so for the remaining intervention cycles. These 6 sessions occur before and after the standard stress reduction program, as explained above.

b. Throughout the entire study, I have been attending weekly to bi-weekly meetings with the study PI and Project Coordinator to discuss overall study issues, including design issues, recruitment, etc.

c. Currently, I am preparing a manuscript reporting on preliminary data related to the study which hopefully will be published. I am working on this with Dr. Jane Teas, another study co-investigator, and Dr. Hebert, the study PI.

CONCLUSIONS

In summary, progress in the first year of this grant has been excellent. All of the deliverables that were promised have been completed successfully, recruitment figures are on track, and retention is excellent. Governance for the study has worked very well with most executive decision making happening in a small working group consisting of Drs. Hebert and Massion and Ms. Susan Druker. In some instances our decisions are provisional on their being broadcast to investigators at UMMC and other sites for final approval. Day-to-day operational issues have been decided mainly in the site coordinator's working group which is chaired by the Project Coordinator/UMASS Site Coordinator, Ms. Susan Druker. Because Susan Druker is a member of both of the functioning working groups, communications within UMMC site and across the four sites have been extraordinarily smooth and efficient. The overall Steering Committee Meeting has occurred twice in the first year. Occasionally, an executive decision has come out of these meetings. However, it has transpired that its main purpose is to provide information to investigators at the other sites and to rekindle enthusiasm in the study. Although there was no place to mention this above, it should be noted that the enthusiasm level for study and the dedication about which people feel regarding their own involvement and involvement in their patients has never been higher in any study with which I have been involved.

One of our major concerns in designing this study concerned issues around the asymmetry of intervention conditions where blinding is not possible. In the years of meetings before we formally proposed this study, we spent more time on this issue than anything else. Our concern was that an obvious imbalance between the intervention conditions would either lead to a low recruitment rate or there would be large differential dropout after women were randomized. With 40% of total recruitment currently completed and having begun the second round of interventions, we can confidently say that this has not been a problem. Currently, we are working on a manuscript that discusses issues around behavioral interventions that cannot be blinded. We feel that the experience of the BRIDGES Study provides practical lessons in how to deal with this ubiquitous, very obvious, and little attended to problem.

We hope that the extraordinary successes of the first year of the BRIDGES Study will continue for the remaining three years. I appreciate the opportunity to convey the excellent progress that we have had to date.